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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/599,877	06/23/2000	Johan Lennerstrand	07691.0004	1424

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EXAMINER	
PARKIN, JEFFREY S	
ART UNIT	PAPER NUMBER
1648	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/599,877	Applicant(s) Lennerstrand, J. And B. Larder
	Examiner Jeffrey S. Parkin, Ph.D.	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *31 Oct 2001* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above, claim(s) *15-19* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-14, 20, and 21* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Detailed Office Action

Status of the Claims

1. Applicants' election with traverse of Group I (claims 1-14) in paper no. 6 is acknowledged. The traversal is based upon the premise that the Office has not demonstrated that the concomitant examination of Groups I-V would constitute an undue burden. Applicants argue that since some of the identified groups have the same or similar classifications that an undue burden is not present. An additional argument was provided suggesting that, at the very least, Groups I and V should be rejoined since they constitute similar subject. Applicants' arguments are not deemed to be persuasive.

Applicants are reminded that establishment of *prima facie* evidence for a serious burden requires the demonstration, by appropriate explanation, of **either** separate classification, separate status in the art, or a different field of search as defined in M.P.E.P. § 808.02. The following items adduce a *prima facie* showing of burden:

1) The inventions of Groups I-V each display separate classifications and a separate status in the art as set forth in the last Office action wherein the following was clearly stated:

> 1. Restriction to one of the following inventions is required under 35 U.S.C. § 121:
>
> a. Group I, claim(s) 1-14, drawn to a method for assessing HIV viral drug resistance to reverse transcriptase (RT) inhibitors, classified in class **435**, subclass **7.4**.
>
> b. Group II, claim(s) 15 and 16, drawn to a method for determining the proper course of therapy for an HIV-infected patient, classified in class **435**, subclass **5**.
>
> c. Group III, claim(s) 17 and 18, drawn to a kit for detecting HIV variants that are resistant to RT inhibitors, classified in class **422**, subclass **61**.
>
> d. Group IV, claim(s) 19, drawn to a method for determining the

mechanisms of action of an RT inhibitor, classified in class **435**, subclass **6**.

e. Group V, claim(s) 20 and 21, drawn to a method for determining the effects of RT mutations on drug resistance, classified in class **435**, subclass **7.6**.

2) The inventions of Groups I-V are each directed towards different subject. Applicants are again directed toward paper no. 5 wherein the following reasons were clearly provided:

> 2. The inventions are distinct, each from the other because of the following reasons:
>
> 3. Inventions I-V are all unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects (refer to M.P.E.P. ¶s 806.04 and 808.01). In the instant case, the various methodologies are directed toward different scientific objectives (e.g., determining drug resistance, planning patient therapy, identifying mechanisms of drug resistance) that utilize different reagents and assay steps. Moreover, the kit of Group III is neither required nor utilized by the methods of Groups I/II/IV/V. Moreover, separate searches will be required for each group identified. Therefore, each invention is clearly drawn toward a different inventive entity.
>
> 4. Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, requirement for independent searches, and recognized divergent subject matter, restriction for examination purposes as indicated is proper. Applicants are required under 35 U.S.C. § 121 to elect a single group for prosecution on the merits. Applicants are also reminded that the claims should be amended, if necessary, to reflect the election.

Accordingly, each invention will generate unique issues regarding novelty, patentability, and enablement.

3) Since the inventions disclosed *supra* are directed towards patentably distinct material, a search for one invention would not necessarily result in the identification of art that is concomitant with that required to address the issues generated by the other inventions. Accordingly, **the original requirement is still deemed to be proper and is therefore made FINAL.** Nevertheless, the

Examiner has decided to rejoin Groups I and V to facilitate compact prosecution. Accordingly, claims 15-19 are withdrawn from further consideration by the examiner, pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention. Claims 1-14, 20, and 21 are currently under examination.

Information Disclosure Statement

2. The information disclosure statement filed 29 August, 2000, has been placed in the application file and the information referred to therein has been considered.

Disclosure

3. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (e.g., see p. 4, lines 10-11). **Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code.** See M.P.E.P. § 608.01.

35 U.S.C. § 112, Second Paragraph

4. Claims 1-14 and 21 are rejected under 35 U.S.C. § 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. M.P.E.P. § 706.03(f). The claims are directed toward a method for determining the level of resistance of HIV to an RT inhibitor. However, the assay only describes steps involving the addition of a wild-type **or** mutant enzyme to a reaction mixture. From this step the RT activity and level of resistance are determined. It is not readily manifest how the level of resistance can be determined in the absence of an appropriate control. For instance, the methodology would require at least two separate reactions, one involving the wild-type enzyme, and the other involving a mutant enzyme. Moreover, in order to assess the level of resistance, an additional

comparison would be required to ascertain how the result obtained with the mutant enzyme compares to other mutants. For instance, a comparison may be required between the test sample and a standardized curve including various mutants with known activities. Appropriate correction and amendment of the claim language, as supported by the disclosure, is required.

5. Claims 1-14 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are directed toward a method of "determining the level of resistance" of an HIV RT to an RT inhibitor. However, it is not readily manifest which specific activities (i.e., primer extension, fidelity, chain-terminating nucleotide removal, etc.) of the RT are being examined to ascertain the "level of resistance". Moreover, it is not readily manifest what type of controls or comparisons are being performed to ascertain the level of resistance. Applicants should amend the claim language to more accurately and clearly describe the invention

6. Claim 14 is also confusing for referencing mutations at codon 69 that are insertions. The preceding claim references specific mutations at a particular amino acid. It is not readily manifest how a single amino acid could contain an insertion. It is either substituted or deleted. If additional amino acids are inserted between this amino acid and another amino acid (i.e., aa 70), this should be clearly set forth in the claim language. Appropriate amendment to the claim language is required.

35 U.S.C. § 103(a)

7. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office

action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

9. Claims 1-3, 5-12, 20, and 21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996). Meyer *et al.* (1999) provides an HIV RT enzymatic assay to examine mutant activity that employs a template, primer, RT inhibitor, and either ATP/GTP or pyrophosphate (see Experimental Procedures, p. 42). The authors reported (p. 35, rt. col.) the following:

> we describe an in vitro assay that reproduces the essential in vivo properties of the AZT resistance mutants. HIV-1 RT containing the D67N, K70R, T215F, and K219Q amino acid substitutions (designated as 67/70/215/219 RT in this report) was much more efficient than WT RT at extending the primer

> past several potential termination sites in the presence of AZTTP when ATP was added to the reaction. Transfer of the AZTMP residue from the primer terminus to ATP to form dinucleoside polyphosphate and unblocked primer was enhanced in the 67/70/215/219 RT.

The authors also noted (see p. 35, last paragraph, rt. col.) that the "Addition of a ribonucleoside triphosphate (ATP) to the reaction mixture provided an acceptor for the nucleotide-dependent primer unblocking activity in which the AZTMP residue from the chain-terminated primer was transferred to ATP to form Ap_4AZT, and the primer was shortened by one residue and was no longer blocked to elongation". The authors finally conclude (see p. 36, rt. col.) "by adding ATP at concentrations likely to be present in intact cells, we have established an in vitro system that reflects the in vivo properties of the 67/70/215/219 mutant virus." This teaching does not disclose an RT assay that employs a detectable dNTP.

However, Ekstrand *et al.* (1996) provide a non-radioactive reverse transcriptase assay that employs 5-bromodeoxyuridine 5'-triphosphate (BrdUTP) as the detectable dNTP (see Materials and Methods, p. 97). The assay described employs an alkaline phosphatase-conjugated anti-BrdU antibody and provides quantitative results. The authors note (see p. 104, last paragraph) "the present paper describes a simple, sensitive and non-radioactive RT assay with kinetic features similar to those observed when the natural dTTP substrate is used."

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the detection format described by Ekstrand *et al.* (1996), in the RT assay provided by Meyer *et al.* (1999), since this provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription.

10. Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ueno *et al.* (1995). The content of Meyer *et al.* (1999) is disclosed in the preceding paragraph. Meyer and colleagues do not describe the utilization of an art-recognized RT activity label such as a radioactive dNTP, although a labeled primer was employed. However, Ueno *et al.* (1995) describe standard HIV RT assays that employ art-recognized labels such as radioactive labeled dNTPs (see pp. 23605-23606, EXPERIMENTAL PROCEDURES, *Materials* and *Product Analysis*). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize a radiolabeled dNTP, as taught by Ueno *et al.* (1995), in the assay of Meyer *et al.* (1999), since this represents a standard and art-recognized means for detecting RT reaction products.

11. Claims 13 and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer *et al.* (1999) in view of Ekstrand *et al.* (1996), as applied *supra* to claims 1-3, 5-12, 20, and 21, and further in view of Larder *et al.* (1999a, 1999b). The combination of references employed *supra* do not disclose the use of HIV RT mutants carrying mutations at amino acid positions 67, 69, and 70, or an insertion between amino acids 69 and 70. However, both Larder *et al.* (1999a, 1999b) publications disclose that HIV-1 RT resistant variants, particularly MNR variants, carry mutations at amino acids 67, 69, and 70, and between amino acids 69 and 70. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the HIV-1 RT mutants described by Larder *et al.* (1999a, 1999b), in the reverse transcriptase assay suggested by Ekstrand *et al.* (1996) and Meyer *et al.* (1999). One of ordinary skill in the art would have been motivated to include these mutant forms of the RT since they naturally develop during the course of antiviral

therapy.

12. Claims 1-3, 5-12, 20, and 21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ekstrand *et al.* (1996). Arion *et al.* (1999) provides an HIV RT enzymatic assay to examine mutant activity that employs a template, primer, RT inhibitor, and pyrophosphate (see p. 15910, MATERIALS AND METHODS, *Analysis of Chain Termination of RT-Catalyzed DNA Synthesis*). The authors suggested (see p. 15908, ABSTRACT) that "HIV-1 resistance to AZT results from the selectively decreased binding of AZTTP and the increased pyrophosphorolytic cleavage of chain-terminated viral DNA by the mutant RT at physiological pyrophosphate levels, resulting in a net decrease in chain termination. The increased processivity of viral DNA synthesis may be important to enable facile HIV replication in the presence of AZT, by compensating for the increased reverse reaction rate." This teaching does not disclose an RT assay that employs a detectable dNTP.

However, Ekstrand *et al.* (1996) provide a non-radioactive reverse transcriptase assay that employs 5-bromodeoxyuridine 5'-triphosphate (BrdUTP) as the detectable dNTP (see Materials and Methods, p. 97). The assay described employs an alkaline phosphatase-conjugated anti-BrdU antibody and provides quantitative results. The authors note (see p. 104, last paragraph) "the present paper describes a simple, sensitive and non-radioactive RT assay with kinetic features similar to those observed when the natural dTTP substrate is used."

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the detection format described by Ekstrand *et al.* (1996), in the RT assay provided by Arion *et al.* (1998), since this provides a rapid, quantitative, and non-radioactive means for

detecting the products of reverse transcription.

13. Claim 4 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ueno *et al.* (1995). The content of Arion *et al.* (1998) is disclosed in the preceding paragraph. Meyer and colleagues do not describe the utilization of an art-recognized RT activity label such as a radioactive dNTP, although a labeled primer was employed. However, Ueno *et al.* (1995) describe standard HIV RT assays that employ art-recognized labels such as radioactive labeled dNTPs (see pp. 23605-23606, EXPERIMENTAL PROCEDURES, *Materials* and *Product Analysis*). Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize a radiolabeled dNTP, as taught by Ueno *et al.* (1995), in the assay of Arion *et al.* (1998), since this represents a standard and art-recognized means for detecting RT reaction products.

14. Claims 13 and 14 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion *et al.* (1998) in view of Ekstrand *et al.* (1996), as applied *supra* to claims 1-3, 5-12, 20, and 21, and further in view of Larder *et al.* (1999a, 1999b). The combination of references employed *supra* do not disclose the use of HIV RT mutants carrying mutations at amino acid positions 67, 69, and 70, or an insertion between amino acids 69 and 70. However, both Larder *et al.* (1999a, 1999b) publications disclose that HIV-1 RT resistant variants, particularly MNR variants, carry mutations at amino acids 67, 69, and 70, and between amino acids 69 and 70. Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the HIV-1 RT mutants described by Larder *et al.* (1999a, 1999b), in the reverse transcriptase assay suggested by Ekstrand *et al.* (1996) and Arion *et al.* (1998). One of ordinary skill in the

art would have been motivated to include these mutant forms of the RT since they naturally develop during the course of antiviral therapy.

Correspondence

15. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

16. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

10 January, 2002